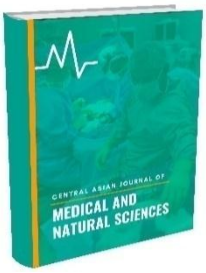
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Significance of Cystatin-S and Galectin-3 Levels in Patients with Chronic Heart Failure

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Annotation: The study of markers - Cystatin C and Galectin 3 is an important clinical and diagnostic role that determines the processes of fibrosis and myocardial remodeling in the early stages of the disease.

Key words: chronic heart failure, cystatin C, galectin 3.

Despite significant advances in the treatment of various cardiovascular diseases, the prevalence of chronic heart failure (CHF) continues to grow [3]. In European countries, this disease is diagnosed in 1-2.6% of the population [17], in the USA - in 5.7 million adults over 20 years old, the prevalence is 2.2% [7]. In the Russian Federation, HF was detected in 7.9 million people, according to other data - in 7% of the population, and almost 70% in people over 90 years old [5]. In Europe, CHF accounts for 5% of all hospital admissions [23]. In the US, CHF results in 1.023 million hospital admissions annually (6.5 million bed days) [18]. In the Russian Federation, among hospitalized patients with cardiovascular diseases (CVD), CHF is the main reason for inpatient treatment in 16.7%. This disease is the most common reason for hospitalization among people over 65 years of age [11]. Moreover, about 50% of patients with CHF are re-hospitalized within 6 months, 20–25% of patients within 30 days after discharge from the hospital [24]. 70% of readmissions are associated with decompensated heart failure [8]. In the future, due to the aging of the population, an increase in the prevalence of cardiac risk factors and an improvement in the survival of patients with various cardiovascular pathologies, a further increase in the number of patients with CHF is expected [10]. By 2030, an increase in the number of patients with CHF by 46% is predicted [16].

CHF is the leading cause of cardiovascular mortality [21]. Mortality in CHF is 4–10.3 times higher than in the general population of the corresponding age, and is comparable to, or even exceeds, mortality from a number of oncological diseases [2]. Five-year mortality in CHF from the moment of diagnosis until the 90s was 60–70% of patients, in recent years there has been a slight but significant decrease to 50% [15]. Annual mortality in CHF is 17.4-33% [19]: in the USA - 250 thousand, in the Russian Federation - 612 thousand people per year [14]. Moreover, mortality in CHF patients with reduced left ventricular ejection fraction (LV EF) is higher than in patients with CHF with preserved LV EF, regardless of age, gender and CHF etiology [13]. In-hospital mortality in CHF is 2-20%. Early

post-hospital (within 30 days after discharge from the hospital) - 11.3% [9]. Mortality in patients with CHF remains high, even despite treatment with ACE inhibitors, beta-blockers, and aldosterone receptor antagonists, which have shown in numerous clinical studies a significant reduction in the relative risk of mortality compared with placebo [20].

In this regard, the objectives of healthcare are to significantly improve the quality of medical care for patients with CHF, prevent the progression of the disease and disability, improve the quality and increase life expectancy.

Currently, the search and study of new biological markers of CHF are relevant, which can be a useful tool for monitoring the effectiveness of pharmacotherapy (personalized medicine), early diagnosis of the disease, prognosis of its clinical outcomes, and play an important role in patient risk stratification. To date, only one CHF biomarker, brain natriuretic peptide (BNP), is widely used in clinical practice. The latter is secreted by ventricular cardiomyocytes as a prohormone and already in the bloodstream is cleaved into a C-fragment (BNP itself) and an inactive N-fragment (N-terminal fragment of the BNP precursor, or NT-proBNP) in a ratio of 1:1 [6]. Determining the level of BNP and NT-proBNP is used to screen for asymptomatic ventricular dysfunction, to diagnose and predict CHF, and to evaluate the effectiveness of therapy. However, the level of BNP and NT-proBNP has a fairly large interindividual scatter of values and depends on gender (in women, the content is higher than in men), age (the content is higher in the elderly), body weight (with increasing body weight, the hormone level decreases), the presence of in a history of renal failure and atrial fibrillation (the content of hormones increases) [12]. In this regard, it seems relevant to search for new CHF biomarkers that can compensate for these shortcomings.

Galectin-3 belongs to the β-galactoside-binding protein family. Due to the presence of a collagen-like domain in its structure, galectin binds to a wide range of extracellular matrix proteins, such as tenascin, fibronectin, and laminin. Galectin-3 is expressed by many cells, including neutrophils, macrophages, mast cells, fibroblasts, and osteoclasts, and is found in the lungs, stomach, intestines, uterus, and ovaries [4]. Galectin-3 has numerous autocrine and paracrine properties. It is responsible for the activation of neutrophils, mast cells and T-lymphocytes, the regulation of adhesion cells, the triggering of apoptosis and angiogenesis. Depending on the cell type and the balance between extracellular and intracellular content, galectin-3 can both inhibit and induce cell growth and differentiation [1]. Galectin-3 also plays an important role in protecting the body against pathogens. It enhances pro-inflammatory signals, possessing chemotactic properties in relation to macrophages and monocytes, induces neutrophil adhesion and release of pro-inflammatory factors of leukocytes and mast cells, and participates in phagocytosis [14]. Galectin-3 is practically not found in cardiomyocytes, while myocardial fibroblasts express its high levels [22]. In recent studies, B. Schroen et al. found a pronounced expression of messenger RNA galectin-3 receptors in a model of arterial hypertension in rats [23]. In subsequent studies, the authors found elevated levels of myocardial galectin-3 in animals with progressive heart failure. Scientists have also observed collagen deposition and myocardial remodeling in response to the introduction of galectin-3 into the pericardial cavity [21]. In addition to the above, recent studies illustrate the role of galectin-3 as a mediator of aldosterone-induced vascular fibrosis [4]. A dose-dependent increase in the expression of galectin-3 in the culture of rat vascular smooth muscle cells was shown in response to the administration of aldosterone for 24 hours. Overexpression of galectin-3, in turn, increased the degree of type I collagen deposition in these cells by 1.6 times. Thus, the data of experimental studies obtained using various CVD models indicate a possible biomarker function of galectin-3, which is an inducer of fibrosis and myocardial remodeling [5].

Of interest is the study by Yu.V. Dubolazova, which included 60 patients with HF with preserved and reduced ejection fraction (EF) of the left ventricle (LV), according to the results of which the level of

galectin-3 in the blood serum of patients with HF with preserved EF significantly exceeded that in patients with HF with reduced EF and had significant correlation with LV EF ($p < 0.05$). These data may indicate a more pronounced myocardial fibrosis in patients with preserved EF, leading to the progression of LV diastolic dysfunction. The author considers it appropriate to determine the level of galectin-3 once, while the combined determination of the level of NT-proBNP and galectin-3 in the blood serum helps to establish the type of heart failure, clarify the severity of its course, evaluate the effectiveness of the therapy, the patient's prognosis and the risk of developing an unfavorable outcome [13].

The short-term predictive value of galectin-3 was studied in the PRIDE study in 209 patients with acute dyspnea admitted to the intensive care unit [12]. Plasma galectin-3 levels in patients with acute HF were initially high. During the 60-day follow-up period, acute HF recurred in 29% of patients (8% of patients died). The area under the ROC-curve of 60-day mortality and recurrence of acute HF for galectin-3 was 0.74 ($p < 0.0001$) compared with 0.67 ($p < 0.009$) for NT-proBNP. Based on these data, a 60-day mortality predictor for galectin-3 was determined to be 9.42 ng/mL (sensitivity 75%, specificity 56%). The overall mortality and recurrence rates of acute HF were highest in patients with a combination of high levels of both galectin-3 and NT-proBNP [11]. Although the diagnostic value of NT-proBNP for HF exceeded that of galectin-3, the latter was a stronger predictor of short-term mortality. In the CARE-HF study, the effect of galectin-3 on the average prognosis of patients with CHF III-IV FC according to NYHA with signs of LV systolic dysfunction and myocardial dyssynchrony according to echocardiography was evaluated. The level of galectin-3 in blood plasma was determined at the beginning and after 3 and 18 months of observation. According to the results of the study, the initial level of galectin-3 was in direct correlation with the rates of mortality and hospitalization due to CHF. Plasma galectin-3 levels >30 ng/ml increased the risk of endpoints (mortality and hospitalization due to CHF) by 2.05 times (relative risk) [16].

Thus, a significant number of studies confirm the possibility of using galectin-3 as a HF biomarker. Additional clinical trials are needed to elucidate the possibility of its use in everyday clinical practice and in the development of new drugs.

In recent years, certain data have been accumulated on the prognostic role of the next marker, cystatin C, in patients with cardiovascular diseases. Cystatin C is a 13 kDa protein that belongs to the family of competitive inhibitors of the lysosomal cystine protease and is synthesized at a constant rate in all nuclear cells [1]. Due to the free filtration of cystatin C in the glomerulus, complete reabsorption and catabolism in the proximal tubules, and the absence of tubular secretion, the plasma concentration of this protein is considered to be completely dependent on GFR. Recent studies have shown, however, that plasma cystatin C concentrations are affected by patient age, body mass index, sex, smoking, and high c-reactive protein (CRP) levels. , taking into account the values of cystatin C, is more correct if the above parameters are included in the calculation. In recent years, chi leveling data of age, gender, ethnicity and major cardiovascular risk factors, the level of cystatin C remained an independent indicator, combined with CVD. These results suggest an association between cystatin C concentration and cardiovascular risk factors, but do not provide sufficient information on the mechanisms responsible for this association. A significant limitation of the studies was their retrospective nature.

The prognostic role of cystatin C in the elderly (65 years of age and older) has been carefully evaluated by Shlipak et al. [20] in the Cardiovascular Health Study [6]. The study included 5201 individuals (1989–1990) and an additional 687 African Americans (1992–1993). From 4637 outpatient elderly patients, frozen blood samples were taken at their follow-up visits in 1992–1993 and information was obtained on cystatin C and creatinine concentrations. Follow-up was carried out by annual clinical examinations and telephone interviews every 6 months and continued until 2001 (median follow-up 7.4 years). The entire cohort was subdivided for each marker of kidney function,

initially into quintiles, then into 7 categories as the 5th quintile was divided into 3 groups. The study revealed that in relation to total mortality and deaths from CVD, the hazard ratio (HR) increased from the lowest to the highest concentration of cystatin C. In addition, in the 7th category, an independent combination of cystatin C values with the risk of myocardial infarction was found, and in the 6th category and category 7 - with a risk of stroke. With regard to the relationship between accepted markers of kidney function and mortality, very high creatinine concentrations and low GFR values were independently associated with overall mortality (categories 7 and 6 and 7, respectively), while only category 7, i.e. with altered GFR, associated with CVD mortality. It is important to note that each quintile of creatinine values and increased cystatin C concentrations was associated with a corresponding increase in mortality. Although the results of this extensive study are of considerable interest, it remains unclear whether the statistical evaluation of individual data in the highest quintile could introduce some bias into the results of the analysis and thereby influence the conclusions of this study.

To assess the prognostic role of cystatin C in patients without clinical evidence of chronic renal failure, researchers in the Cardiovascular Health Study prospectively assessed the combination of cystatin C concentrations and the risk of cardiovascular and renal outcomes in elderly individuals with an established GFR ≥60 ml •min - 1 •(1.73 m2) – 1 [24,25,26], observed over 9.3 years (median). The final observation points were death from any cause, death as a result of damage to the cardiovascular system, heart failure, myocardial infarction, stroke. Of the 4663 observed individuals, 1004 (22%) had chronic kidney damage, 3659 (78%) did not have kidney damage. In individuals with GFR ≥ 60 ml • min - 1 • (1.73 m2) - 1 cystatin C concentrations showed a strong association with each outcome, while creatinine concentrations were weak predictors of death from cardiovascular causes. Among 2508 individuals without kidney damage, those examined with cystatin C concentrations of 1 mg/l and above had a higher risk of developing kidney damage than patients with low cystatin C concentrations (followed for 4 years). These results are significant because patients with advanced kidney disease had a significantly higher risk of death than death from cardiovascular causes and heart failure. According to the authors, these results suggest that elevated cystatin C concentrations are observed during the preclinical stage of kidney disease, which is more characteristic of the elderly population (39%) and is associated with an unfavorable outcome. The results of this extensive study indicate the superiority of cystatin C over other markers of renal function as a marker of both renal dysfunction and cardiovascular risk.

In conclusion, it should be noted that an increase in the concentration of cystatin C presumably serves as a marker of chronic kidney damage and cardiovascular risk. If this is confirmed, the role of cystatin C as an early sensitive marker of kidney function would have important clinical implications. Perhaps the found reliable method for the early diagnosis of kidney dysfunction will provide more accurate and effective case management and the development of strategies for cardiovascular risk stratification and prevention. Large, well-designed prospective studies in patients without renal dysfunction are needed to fully elucidate the relationship between high cystatin C concentrations and cardiovascular risk.

Thus, further study of early markers in the prediction of heart failure seems to be quite reasonable and promising. We have not found any literature data on the role of the above markers in combination in patients with CHF. The conducted literature review shows that the study of these markers is an important clinical problem that requires further study, clarification of the mechanisms of development and its influence on the prognosis, as well as on the course of the disease.

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